Summary Basis for Approval

BLA: #96-0486, Supplement 97-0106

Drug License Name: Interferon alfacon-1

Drug Trade Name: Infergen™

Manufacturer: Amgen, Inc.
1840 Dehavilland Drive
Thousand Oaks, CA 91320-1789

BLA received April 11, 1996; filed May 21, 1996

I. Indication for Use

Interferon alfacon-1 (Infergen™) is indicated for the treatment of chronic hepatitis C virus infection in patients 18 years or older with compensated liver disease who have anti-HCV serum antibodies and/or the presence of HCV RNA. Other causes of hepatitis, such as viral hepatitis B or autoimmune hepatitis should be ruled out prior to initiation of therapy with Infergen. In some patients with chronic HCV infection, Infergen normalizes serum ALT concentrations, reduces serum HCV RNA concentrations to undetectable quantities and improves liver histology.

II. Dosage Form, Route of Administration, and Recommended Dosage

Interferon alfacon-1 is supplied as a liquid in a single-use vial containing 9 micrograms (mcg) or 15 mcg of interferon alfacon-1 formulated in 100 mM sodium chloride and 25 mM sodium phosphate, pH 7.0. There is no preservative. The recommended dosage of interferon alfacon-1 for the treatment of chronic hepatitis C is 9 mcg administered subcutaneously three times per week (TIW) for 24 weeks. Patients who tolerated previous interferon therapy and did not respond or relapsed following its discontinuation may be subsequently treated with 15 mcg of Infergen TIW for 6 months. Patients should not be teated with 15 mcg of Infergen TIW if they have not received, or have not tolerated, an initial course of interferon therapy.

III. Manufacturing and Controls

Interferon alfacon-1 is derived from a synthetically constructed gene composed primarily of the consensus amino acids at each position in the human alpha interferon family. It is a single chain protein of 166 amino acids (≈19,500 Daltons) produced in E. coli. Pairwise comparisons of nonallelic subtypes of human interferon alpha demonstrate differences of 2-23% (85 of the 166 amino acids are conserved among all subtypes). The consensus sequence differs from interferon alfa-2 at 20/166 amino acids (88% homology), and has approximately 34% homology with human interferon-β. Interferon alfacon-1 possesses a significantly higher (5-10X) specific activity in several in vitro systems than other known recombinant and natural IFNs. Bulk product is manufactured in [redacted], at Amgen in Thousand Oaks, CA, and formulation and

filling is performed at the Amgen Puerto Rico (APR) facility in Juncos, Puerto Rico (the latter is already licensed). The product is supplied in a sterile liquid dosage form as single use vials containing 9 ug interferon alfacon-1 in 0.3 ml 100 mM NaCl and 25 mM $NaPO_4$.

Manufacturing Summary

Filtered purified bulk produced in a multiproduct manufacturing facility at Amgen in Thousand Oaks, CA. The interferon alfacon-1 gene was cloned into an expression vector and the construct was transformed into the ——— to create the production strain. Following fermention, cells are collected and cell paste stored for QA testing and further processing. End of fermentation (cell paste) QA tests include bioburden and product yield testing. In-process controls for fermentation include testing for contamination, viability, protein concentration, genotype verification, plasmid retention, paste yield, and continuous monitoring of pH, temperature, and dissolved oxygen during the fermentation.

Processing begins with cell lysis, centrifugation, solubilization, oxidation and refolding, precipitation, and clarification, followed by chromatography steps and filtration of purified bulk. The final column is eluted in the formulation buffer (———). The eluate is diluted to ——— QA testing precedes further formulation (dilution), filtration and filling at APR. Formulation consists of dilution (to 0.03 mg/ml) of interferon alfacon-1 purified bulk ——— in (——— followed by sterile filtration (——— prior to filling. Formulated bulk is stored at ——— Filtration occurs within — hours of dilution. In-process controls for purification include monitoring of critical process parameters such as homogenizer pressure, time and temperature limits, bioburden, chromatogram records, and process yield.

Interferon alfacon-1 is used for parenteral administration in liquid form in a single-use vial for 0.3 ml deliverable drug at 0.03 mg/ml. Each vial contains 9 μg interferon alfacon-1, 1.77 mg NaCl (100 mM), and 1.14 mg $NaPO_4$ (25 mM, pH 7.0). There are no preservatives added.

Development of production strain for interferon alfacon-1

The interferon alfacon-1 coding sequence was derived from a synthetic construct in which most of the codons encoded consensus amino acids from all of the known human interferon alpha sequences. The interferon alfacon-1 sequence consists of the most common amino acid at each position, with exceptions for restriction site engineering. The amino-terminal methionine is not IFN-derived, so that the ——— at position — is actually considered position —. There is no Working Cell Bank (———). The MCB was checked for contamination by subjecting the last vial filled and 10 randomly selected vials to microbial tests for contaminant strains of bacteria and phage. Validation of plasmid stability has been confirmed by continuous monitoring of peptide mapping and N-terminal sequence of end-of-production protein, complete DNA sequencing of interferon alfacon-1 gene at end of fermentation and at --

Extended fermentation cell paste was analyzed for plasmid retention and product yield and conformed to specifications for cell paste. Product from extended fermentation was analyzed by peptide mapping and N-terminal sequencing and also met specifications for interferon alfacon-1 bulk.

Process Validation

Six purified bulk lots derived from ___ cell paste lots were used for validation of the following: 1. Host cell contaminants and process additives are consistently reduced; 2. The process produces interferon alfacon-1 that meets specifications for purity and identity; 3. Process yields are consistent. Specifications used for the interferon alfacon-1 consistency included bioactivity, RP-HPLC, SDS-PAGE, and peptide mapping.

In-Process and Final Product Testing

Product sampling for specification testing occurs at: fermentation cell paste, filtered purified bulk, sterile formulated bulk, and final vial. Cell paste is tested for product concentration, plasmid retention, genotype, cell mass, and contamination. Purified bulk testing includes protein and bioassay, LAL, pH, sterility, and several biochemical parameters (reversed-phase HPLC, size exclusion HPLC, NH_2-terminal sequence, peptide mapping, SDS-PAGE, and Western blot analysis). Sterile formulated bulk tests are for protein, LAL, pH, and sterility. Final product is tested for protein and bioassay, pH, LAL, Western blot, chloride and phosphate, volume, sterility, and appearance.

Reference Standards

The current in-house reference standard was calibrated against both the NIAID reference standard Ga-23-902-530 (leukocyte, Sendai) and the more recent WHO First International Standard 83/514 (rHuIFN α±1 (D)). Both of those standards were calibrated against the WHO 69/19 First International Standard (leukocyte, Sendai). With the original 69/19 standard, the specific activity of the reference lot was ≈4 x 10^8 in both antiviral and antiproliferative assays. Using the new recombinant WHO standard (83/514), however, yielded a measure of 10^9 U/mg in both assays.

Interferon alfacon-1 Characterization

Extensive biochemical and biophysical characterization of interferon alfacon-1 has been performed. These data include: complete amino acid sequence determination by sequencing of peptides and mass spectrometry; peptide mapping amino-terminal isoform analysis by isoelectric focusing, anion exchange chromatography, and reverse phase chromatography (RP-HPLC); RP-HPLC for analysis of other variants; size exclusion chromatography (SEC) and laser light scattering; SDS polyacrylamide

gel electrophoresis; circular dichroism; fluorescence spectroscopy; acid sensitivity; and UV absorptivity (calculation of extinction coefficient). Of these, RP-HPLC, and peptide mapping provide the most sensitive measures of the presence of variants in the product.

Product Stability

Expiry periods have been set for the following at 2-8°C: formulated bulk for [redacted] hours, filtered purified bulk for [redacted] months, final product for 24 months. Six purified bulk and seventeen final vial lots are currently on the stability program. Stability assays are performed for several biological and biochemical parameters in a comprehensive stability program at -70°C, -20°C, 4°C, and 37°C. Experimental stability data to simulate shipping conditions, freeze-thaw, temperature cycling have also been performed. No significant differences have been observed by any parameters tested. Retention samples from each lot are stored for at least one year beyond expiry. There is an approved stability test protocol that will be used for assuring stability of bulk and final lots of interferon alfacon-1.

Storage and Shipment

Filtered, purified bulk is stored in autoclavable polypropylene containers labeled with product name, specification #, lot #, mass, volume, contents, and QC release status, for up to 6 months at 2-8°C. Product is shipped to APR by commercial air express. Formulated bulk is stored at APR for a period not to exceed 24 hrs at 2-8°C. Filled final vials are stored at APR under QA control until finished. Finished (labelled and packaged) vials are shipped back to Amgen TO and placed in quarantine storage at 2-8°C until release.

Establishment Inspection

A concurrent pre-license and biennial inspection was performed at the bulk manufacturing facility in Thousand Oaks, CA on October 21-25, 1996. The pre-license inspection covered manufacturing facilities in Building 4 and associated quality control/assurance facilities used for the analysis and validation of Infergen manufacture. The Amgen Puerto Rico filling facility in Juncos, Puerto Rico was inspected on January 27-31, 1997. Both facilities were found to be in compliance with current good manufacturing practices.

Environmental Impact

Two environmental assessment reports were filed for the bulk production and distribution facilities and for the APR facility. Fermentation is performed under BL 1-LS containment conditions. Primary effluent to sewers is waste growth media and cleaning streams (primarily NaOH and H_3PO_4). No significant environmental effect is anticipated to result from the production or use of interferon alfacon-1. The manufacture, testing, and distribution of the licensed product does not generate pollutants or materials considered to be biohazards. Materials released into the sewer system are expected to be biodegraded in the wastewater treatement plant

and will not create significant environmental impacts. All other waste materials are disposed of in accordance with state and local environmental requirements.

Assay Validation and Analytical Methods

Validation reports and analytical methods were submitted and reviewed for the following tests: product concentration (cell paste), protein assay, bioassay, LAL, N-terminal sequencing, RP-HPLC, peptide mapping, SDS-PAGE, Western blot, chloride and phosphate analyses, and SEC-HPLC.

IV. Pharmacology/Toxicology

Introduction

The safety, biochemical, and pharmacologic activity of INFERGEN was evaluated in Golden Syrian hamsters, cynomolgus and Rhesus monkeys, rabbits, rats, and guinea pigs *in vivo*, and in cell lines derived from humans, mice, rats, rabbits, cats, dogs, guinea pigs, Rhesus and African green monkeys *in vitro*. Using *in vitro* anti-viral cytopathic effect assays, INFERGEN was found to have significant, viral protective effects only in cell lines from Rhesus monkeys and Golden Syrian hamsters. Because of the species specificity of CIFN in these assays, the *in vivo* pharmacokinetic, acute, and repeat-dose toxicity testing were conducted in Golden Syrian hamsters and the Rhesus monkey.

Pharmacokinetics

Pharmacokinetic studies of INFERGEN in hamsters and Rhesus macaques demonstrated similar absorption and elimination profiles after either s/c or i/v injection. Peak serum concentrations in Syrian hamsters and in Rhesus monkeys were reached 1 and 4 hours, respectively, after a single, subcutaneous injection. Systemic exposure, as calculated from the AUC from time zero to 24 h was increased in a dose-related fashion, was approximately linear in relation to dose, and was similar for both the i/v and s/c routes in both species. Bioavailability by either route was approximately 80 to 100% in both Syrian hamsters and macaques. Clearance was mainly via renal tubular excretion and elimination, and averaged 1.99 mL/minute/kg in golden Syrian hamsters and 0.71 to 0.92 mL/minute/kg in the Rhesus monkeys, resulting in an approximate $t\frac{1}{2}_{elim}$ of 4 to 6 hours.

Toxicology Testing

INFERGEN has pharmacologic and toxicologic profiles similar to other type I interferons; major findings in Rhesus monkeys after repeated s/c dosing at 1, 3, 10, 30, or 100 µg/kg/day of INFERGEN included decreased food consumption and weight loss, slight to moderate decreases

in platelet and leukocyte counts, and enlargement of regional (inguinal, iliac, axillary) lymph nodes. No local irritation and/or inflammation at the sites of injection were noted. The decrease in platelets and leukocytes were related to the dose of INFERGEN administered, and were only evident during the first one to two weeks of treatment. All changes were reversible during 14 to 28 d recovery periods, with the exception of the lymphadenopathies in several animals. Similar changes in appetite, total body weight gain and hematologic profiles were noted in Golden Syrian hamsters receiving INFERGEN at doses of up to 100 µg/kg/day, for periods of up to 6 months. Histologically, the most consistent finding was evidence of subcutaneous and/or intramuscular hemorrhage at the injection site, without evidence of either acute or chronic inflammation in both hamsters and Rhesus monkeys treated for 14 to 90 days with INFERGEN. Sporadic increases in lymphoid hyperplasia, liver vacuolization, and enlargement of the liver and/or spleen were noted in animals of both species, without an apparent, significant dose-relationship or clinical sequelae in studies of less than one month in duration. The NOAEL for INFERGEN in the Rhesus monkey was 1 µg/kg/day, and for the hamster was 10 µg/kg/day, administered for 14-28 days. A loss of detectable interferon activity in the serum and development of neutralizing antibody activity was noted at the end of treatment period in all repeat-dose studies, and antibody titers continued to increase during the recovery phase. There was no apparent dose-relationship in either incidence or titer of antibody development induced in the hamsters. Rhesus monkeys did display antibody development in one study which correlated with both the dose and duration of INFEGEN administered.

Reproductive Toxicology

The reproductive and developmental toxicities of INFERGEN were tested in male and female hamsters, and in female Rhesus monkeys. INFERGEN treatment at doses of 30 or 100 µg/kg/day in the hamsters had no effects on male fertility, mating indices, or the percentage of female hamsters pregnant in a segment I evaluation of fertility and general reproductive function. At 100 µg/kg/day, INFERGEN treatment caused significant increases in early resorptions and decreased litter sizes, indicative of embryolethal effect. Similar embryolethality and fetal losses were observed in pregnant Syrian Golden hamsters treated with either 30 or 150 µg/kg/day INFERGEN in a harmonized segment II/III reproductive study. There were no apparent effects on growth, development, behavior, onset of sexual maturity, or mating or reproductive function in the F1 offspring of the INFERGEN-treated dams. Segment II reproductive toxicity studies in cynomolgus and Rhesus monkeys confirmed the embryotoxicity of CIFN, when animals were treated with 3 to 30 µg/kg/day INFERGEN during the critical period of organogenesis (GD20-GD50). Treatment with INFERGEN at these dose levels was found to increase the incidences of spontaneous abortions and/or fetal deaths in a dose- and time-dependent fashion. The incidence of fetal loss was 10%, 10%, 40% and 80% for Rhesus monkeys treated with 0, 1, 3, or 10 µg/kg/day CIFN, respectively, and was 33% and 100% for pregnant female cynomolgus monkeys treated with 10 or 30 µg/kg/d, respectively. The NOAEL for toxicity to reproduction was 1 µg/kg/day, administered daily from GD20-50 in the Rhesus monkey, and 10 µg/kg/day in the Golden Syrian hamsters when administered either from d -15 to GD7 or from GD5 to GD15.

Summary and Conclusion

In summary, the safety, biochemical, and pharmacologic activity of INFERGEN in Golden Syrian hamsters, cynomolgus and Rhesus monkeys are similar to other type I interferons. Major findings included high degrees of systemic exposure after subcutaneous injection, with approximately 100% of the dose absorbed, and an elimination half-life of approximately 2 to 6 hours. Toxicity was limited to decreased food consumption and weight loss, slight to moderate decreases in platelet and leukocyte counts, and lymph node enlargement, with no local irritation and/or inflammation at the site of injection. These effects were dose-related, and for the most part were reversible within a 14 to 28 day recovery period. The NOAEL for INFERGEN in the Rhesus monkey was 1 μg/kg/day, and for the hamster was 10 μg/kg/day, administered for 14-28 days. Longer administrations were limited by the development of neutralizing antibody activity. INFERGEN treatment at doses of up to 100 μg/kg/day had no adverse effects on male fertility, mating indices, or the percentage of female hamsters pregnant in a segment I evaluation. At doses of 30 to 150 μg/kg/day, INFERGEN treatment of pregnant female hamsters caused significant increases in early resorptions and decreased litter sizes, indicative of embryolethal effect. Similar embryolethality and fetal losses were observed in pregnant cynomolgus and Rhesus macaques treated with 3 to 30 μg/kg/day of INFERGEN during the critical period of organogenesis (GD20-GD50). The NOAEL for toxicity to reproduction was 1 μg/kg/d, administered daily from GD20-50 in the Rhesus monkey, and 10 μg/kg/d in the Golden Syrian hamsters when administered either from d -15 to GD7 or from GD5 to GD15.

In conclusion, these data adequately represent the pharmacology, pharmacokinetics, and toxicities associated with type I interferons, and support the safety of this product for licensure for use in chronic hepatitis C infection. The abortifacient effects of INFERGEN have been clearly represented in the proposed package insert, and the biologic has been assigned a pregnancy category "C", which is appropriate for these data.

V. Clinical

Introduction: Three clinical trials were conducted to establish the safety and efficacy of interferon alfacon-1 (Infergen) in the treatment of chronic HCV infection. The first trial, CIFN-9105, was a Phase 1/2 dose-ranging study to determine the tolerability and preliminary efficacy of Infergen. The second study, CIFN-9210, was a pivotal Phase 3 study using two dosages of Infergen in interferon-naive patients with chronic HCV infection, in which patients were treated for 24 weeks and then observed for an additional 24 weeks to determine rates of sustained response, as measured by normalization of ALT concentration. A third study, CIFN-9223, was conducted to determine the safety and efficacy of subsequent treatment with a higher dose of Infergen for those patients in study CIFN-9210 who had failed to maintain a sustained response with initial therapy.

Data from trials CIFN-9105 and CIFN-9210 were submitted as BLA 96-0486. Data from trial

CIFN-9223 were submitted as Supplement 97-0106 to BLA 96-0486.

The primary endpoint for trials CIFN-9210 (initial treatment) and CIFN-9223 (subsequent treatment) was normalization of ALT concentration at the end of interferon treatment. However, the sponsor and CBER recognized that a more appropriate measure of efficacy, as determined by use of interferon in the medical and scientific communities, was sustained normalization of ALT concentration following 24 weeks of observation after completion of drug treatment. This modified endpoint was adopted as the primary measure of efficacy to evaluate data from the above-mentioned BLA and Supplement.

A. Phase I/II clinical trial: A single center, single investigator, dose-escalating trial was conducted to determine the maximal tolerated dose (MTD) of Infergen. Ten patients were enrolled per dosage arm, with doses of 3 μg, 6 μg, 9 μg, 12 μg, 15 μg, 18 μg, and 24 μg Infergen scheduled to be tested. At any dose, if dose limiting toxicity (DLT) occurred in 50% of subjects (i.e. 5/10) then further dose escalation would be halted and that dose at which 50% DLTs had occurred would be declared the MTD. Patients were treated for 24 weeks with a TIW sc regimen and were followed for an additional 24 weeks after cessation of treatment. DLTs occurred in two dosage groups: at 12 μg (n=2) and at 15 μg (n=5); therefore, 15 μg Infergen was declared the MTD dose. Adverse events leading to withdrawal from study were qualitatively similar to adverse events previously associated with interferon therapy.

Efficacy at end-of-treatment (24 weeks) and end-of-observation (48 weeks) was evaluated for all dosage arms. Of the 55 patients that were enrolled in the five dosage arms, serum ALT concentrations were normalized in 20/55 (36%) at the end of the treatment period, and 11/55 (20%) of patients had sustained normalization of ALT at the end of the observation period (sustained response). Serum HCV RNA concentration was undetectable (< 100 copies/ml) in 28/55 patients (51%) at the end of the treatment period, and was undetectable in 13/55 patients (24%) at the end of the observation period.

B. Phase 3 clinical trial for initial therapy with Infergen: A Phase 3 randomized, double-blind, multicenter study in patients with chronic HCV infection was conducted in 41 sites in the US and Canada. Based upon results from the Phase I/II trial, Infergen dosages of 3 μg and 9 μg were chosen, and compared to 3 MIU Interferon alfa-2b (Intron A™, Schering Corporation, Kenilworth, NJ), which corresponded to approximately 15 μg Intron A. Randomization was carried out on a 1:1:1 basis, and a total of 704 patients were enrolled in the study. Patients were 18 years or older, had compensated liver disease, tested positive for HCV RNA, and had elevated serum ALT concentrations averaging > 1.5 times the upper limit of normal. Staging of chronic liver disease was confirmed by a liver biopsy taken within one year prior to enrollment. Other causes of liver disease were ruled out prior to randomization. Notable exclusion criteria were decompensated liver disease, thyroid abnormality, or history of depression.

Efficacy: Efficacy of Infergen therapy was assessed on an intent to treat basis and was determined by measurement of serum ALT concentrations at the end of therapy (24 weeks) and following 24

weeks of observation after the end of treatment (sustained response rate). Serum HCV RNA was also assessed using PCR methodology with a lower limit of sensitivity of 100 copies/ml. Liver histology was assessed by comparing the histology activity index (HAI) score of a pretreatment biopsy specimen with the HAI score from a specimen obtained 24 weeks after cessation of interferon therapy.

Sustained response rates by ALT normalization and HCV RNA reductions to below detectable limits are shown below. Treatment with Infergen 9 μg demonstrated a similar efficacy profile when compared to treatment with IFN α-2b, while treatment with Infergen 3 μg demonstrated efficacy that was substantially lower than the other two dosage arms.

Response Rates (95% CI) by ALT Normalization and HCV RNA Reductions to Below Detectable Limits

	End of 24 Week Treatment		End of Observation (Sustained Response Rate)	
	Infergen 9 mcg	**IFN α-2b 3 MIU**	**Infergen 9 mcg**	**IFN α-2b 3 MIU**
Normalized ALT	39% (33%, 46%)	35% (29%, 41%)	17% (12%, 22%)	17% (13%, 22%)
HCV RNA Negative	33% (27%, 39%)	25% (19%, 31%)	9% (6%, 14%)	8% (5%, 13%)

In the pivotal study, liver biopsies were taken at baseline and at the end of posttreatment observation. Similar improvement in liver histology, assessed by HAI score, was observed in the 9 μg Infergen (68%), 3 μg Infergen (63%), and IFN α-2b (65%) dosage arms.

Safety: Adverse events (AE) were reported in a large percentage of patients, consistent with prior experience with the use of interferon for the treatment of HCV. AE were assessed with regard to severity and seriousness. "Flu-like" symptoms (headache, arthralgia, myalgia, fever, chills) were common and were generally treated with premedication prior to injection of Infergen. Other less frequent events required dose interruption or dose reduction and are summarized below in narrative format, with no ranking by severity or cause for dose-limiting toxicity: injection site pain (23%), allergic-type reaction (7%), hypertension (5%), palpitation (3%), insomnia (39%), dizziness (22%), paresthesia (13%), amnesia (10%), hypesthesia (10%), confusion (4%), abnormal thyroid test (9%), abdominal pain (41%), nausea (40%), anorexia (24%), dyspepsia (21%), vomiting (12%), granulocytopenia (23%), thrombocytopenia (19%), leukopenia (15%), lymphocytosis (5%), liver tenderness (5%), hepatomegaly (3%), musculoskeletal pain (14-42%,

depending on body region), depression (26%), anxiety (19%), labile emotions (12%), abnormal thinking (8%), agitation (6%), dysmenorrhea (9%), infection (3%), pharyngitis (34%), URI (31%), cough (22%), sinusitis (17%), rhinitis (13%), respiratory tract congestion (12%), epistaxis (8%), dyspnea (7%), alopecia (14%), pruritus (14%), rash (13%), conjunctivitis (8%), and abnormal vision (3%).

Withdrawals from study during treatment with 9 μg Infergen occurred in 45 patients (6.4%) and were due to AE that had been attributed previously to treatment with alpha interferons. Depression, reported in 26% of patients who received 9 μg Infergen, was the most common AE resulting in withdrawal, and the remaining AE resulting in study withdrawal were heterogenous and no pattern of related events was seen. In the 9 μg Infergen dose arm, 16 patients (6.9%) were withdrawn from therapy, of which 9 patients (3.9%) were withdrawn for psychiatric AE. Overall, 54% of patients in the 9 μg Infergen arm complained of depression, but only 2% of these AE were considered serious. No deaths which occurred on study were attributable to interferon usage.

Dose reductions in the 9 μg Infergen arm were reported in 43/232 (18.6%) of patients, of which 34 patients (14.7%) were dose-reduced secondary to clinical AEs and 9 patients (3.9%) were dose-reduced secondary to laboratory AEs. The most commonly reported events resulting in dose reductions were fatigue, pain, fever, headache, diarrhea, abdominal pain, nausea, myalgia, depression, and nervousness. The most common laboratory abnormality requiring a dose reduction was thrombocytopenia. The median time to onset for the first dose-limiting toxicity was 56 days in the 9 μg Infergen arm, as compared to 56 days for patients treated with IFN α-2b.

Antibody formation: Serum antibody levels to interferon were measured using both an Infergen-binding radioimmunoassay and an IFN α-2b-binding ELISA. A similar number of patients developed a positive antibody response to either 9 μg Infergen (11%) or to 3 MIU IFN α-2b (15%). Development of an antibody response was not associated with decreased efficacy, as ALT normalization rates were equivalent among patients who formed antibodies and patients who had no detectable anti-interferon antibodies. The most frequently observed time to first antibody response was week 16 of treatment, with a subsequent decline in antibody titer observed during posttreatment observation.

C. Subsequent treatment of nonresponsive/relapsed patients with Infergen: Subsequent treatment with 15 μg Infergen was evaluated in an open-label clinical trial in 107 patients who had failed initial therapy with either 9 μg Infergen or 3 MIU (approximately 15 μg) IFN α-2b. Of these patients, 74/107 had failed to normalize ALT concentrations during either the initial treatment period or the posttreatment observation period, while 33/107 achieved a normal ALT concentration during initial treatment, but experienced relapse (return of abnormal ALT concentration) during posttreatment observation. Efficacy was assessed in the same manner in these patients as in the pivotal trial. Serum ALT and HCV RNA response rates to subsequent treatment with 15 μg Infergen are shown below with 95% CI indicated in parentheses.

Sustained Response Rates in Patients Receiving Subsequent Treatment

	End of Observation (Sustained Response Rate)		
	Overall	Nonresponders	Relapsers
Normalized ALT	15% (9%, 23%)	8% (3%, 17%)	30% (16%, 49%)
HCV RNA Negative	9% (5%, 17%)	3% (0%, 9%)	25% (11%, 43%)

In general, the frequency of adverse events observed upon subsequent treatment with 15 μg Infergen was less than the rate observed during initial therapy. This is inconsistent with data generated in the Phase 1/2 study (e.g. 15 μg Infergen was defined at the MTD) but might be explained by enrollment of subjects with prior experience with interferon therapy and/or decreased reporting of somatic complaints by patients or investigators. The incidence of psychiatric AE, particularly depression, was lower than reported with initial therapy. It is unlikely that the safety profile for treatment with 15 μg Infergen is superior to the safety profile for treatment with 9 μg Infergen in interferon-naive subjects, given the Phase 1/2 data and consistent findings from other studies with alpha interferons which demonstrate a direct relationship between the dose of interferon and its safety profile.

Notably, however, treatment with 15 μg Infergen was associated with a higher incidence of neutropenia than was reported with initial therapy (42% versus 23%), but neutropenia was transient and was not associated with a higher incidence of infections at the nadir in neutrophil count. Leukopenia was also increased in patients receiving 15 μg Infergen. Overall, one or more dose reductions were required in 33% of patients who received 15 μg Infergen for subsequent treatment, and approximately half did so within the first 8 weeks. Six patients (5.6%) were withdrawn due to intolerable AE and an additional seven patients (6.5%) had serious AE during either the treatment period or posttreatment observation period.

Due to the frequency and severity of AE experienced with Infergen therapy, it is recommended that patients who do not tolerate initial standard therapy (e.g. 9 μg Infergen) should not receive therapy with 15 μg Infergen.

VI. Phase IV Commitments

As a condition of approval, Amgen was requested to perform the following studies:

1. Provide a validation report for, and stability data from, the revised method for the reversed phase HPLC assay, [redacted]

2. Provide a validation report for the [redacted] antiproliferative bioassay, [redacted]

3. Provide a validation report for the revised peptide mapping procedure [redacted]

4. Continue to trend changes in the relative levels of [redacted] and correlate these changes with all measured fermentation parameters and will attempt to establish alert limits for these variants to signal exceptional changes in the fermentation process.

5. Provide a validation report with interferon alfacon-1 for the isoelectric focusing procedure used in stability testing.

6. Provide a revised SOP for the the establishment of interferon reference standards and a certificate of analysis for the secondary reference standard currently in use for interferon bioassays.

7. Conduct a randomized, multicenter, controlled study to assess the safety and efficacy of interferon alfacon-1 in 175 interferon-naive patients for six months versus 175 interferon-naive patients for 18 months.

VII. Labelling

Containers will be labelled with the proprietary name INFERGEN®9, referring to the 9 μg dose, and with the USAN name interferon alfacon-1. INFERGEN is not known to be in conflict with any other product tradename. Container and package labels comply with 21 CFR 610.60-62 and 201.56-57, and include the concentration of product (9 μg/3 ml), notation as a single-use vial, and instructions to refrigerate the product at 2-8°C. A copy of the approved package insert is attached.